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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/200,791	11/30/1998	THOMAS M. BEHR	018734/0161	9799

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/200,791	BEHR ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-21,23-29 and 31-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-21,23-29 and 31-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/30/04 has been entered.

2. It is noted that the response filed 8/23/04 states that claims 1-9, 11-21, 23-29, 31-37, 40-42 as presented here are in the form previously indicated as allowable in the Notice of Allowability mailed December 22, 2000. In response to this, upon further consideration the following Office Action is being sent out.

3. Claims 1-9, 11-21, 23-29, 31-41 are pending.

Claims 1, 2, 18-19 have been amended.

Claims 38-41 have been added.

Claims 1-9, 11-21, 23-29, 31-41 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. This Office Action contains NEW GROUNDS of rejections.

Claim Objection

6. Claim 38 is objected to because the term "polylysine" should be "poly-lysine" as recited in other claims.

Appropriate correction is required.

Priority

7. The instant application is a CIP of 08/407899 filed 3/21/95 (now US Patent 5,843,894). Claims 1 and 18 in the instant application recite the limitation of a method of reducing kidney retention of a protein conjugate. This limitation is not seen in the 08/407899 application. The 08/407899 application is directed to reducing renal uptake of antibody and antibody fragment conjugates which is a species of the now claimed genus of protein conjugates. The species of antibodies does not support the genus of just any protein conjugate. In addition, the glycoprotein conjugates and lipoprotein conjugates do not have support in the 08/407899 application (see claim 2 in the instant application). As such the claims are granted the priority date of the instant application, 11/30/98.

Rejections Withdrawn

8. The rejection of claims 1-21 and 23-37 under 35 U.S.C. 103(a) as being unpatentable over Behr et al (Cancer Research 55:3825-3834, 1995), and further in

view of Grey et al (U. S. Patent 5,380,513, issued 1/10/95, IDS #4) and Raines et al (U.S. Patent 5,840,296, filed 10/15/97) is withdrawn in view of the new grounds of rejections set forth below.

The following are NEW GROUNDS of rejections

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 38 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 38 has been added (not entered in the response filed 2/14/03 but entered now upon filing the RCE) and recites the limitation of a method comprising administering to a patient a "cytotoxic agent or imaging isotope" and additionally administering D-lysine or poly-lysine. The response filed 2/14/03 stated that the generic phrase in new claim 38 is the exact language contained in the '899 application and one skill in the art reading the specification as a whole would readily understand that applicants possessed a generic scope extending to all such cytotoxic or imaging agents that are susceptible to renal uptake (see page 3 of response). The response has been carefully considered but is deemed not to be persuasive. The instant specification is

directed to protein conjugates comprising cytotoxic or imaging agents and '899 specification is directed to antibody or antibody fragment conjugates comprising cytotoxic or imaging agents. There is no support in either application for methods using the cytotoxic or imaging agents alone that are not conjugates of protein or antibodies in a method with administration of D-lysine or poly-lysine. Applicant is required to provide specific support for the limitation in the application as originally filed of remove the limitation from the claim.

11. Claims 19 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing kidney retention of a protein conjugate of a cytotoxic or imaging agent and administering poly-lysine or D-lysine having a molecular weight of 1-60kD, does not reasonably provide enablement for a method of reducing kidney retention of only a cytotoxic or imaging agent or just any metabolic product or peptide, polypeptides, glycoproteins, lipoproteins, antibodies or antibody fragments and administering poly-lysine or D-lysine having a molecular weight of 1-60kD. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence

or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of reducing kidney retention with a protein conjugate that is a metabolic product of a peptide, polypeptide, glycoprotein, lipoprotein, antibodies or antibody fragments or a cancer therapeutic or diagnostic method of administering a cytotoxic agent or imaging agent and D-lysine or poly-lysine to reduce kidney retention of the agent. The specification discloses reducing the renal uptake of protein conjugates, in particular antibody conjugates by adding D-lysine, poly-lysine (see page 3). The specification does not enable the reduction of renal uptake of agents not conjugated to a protein or peptide or that just any metabolic products which are the protein conjugate that are reduced in renal uptake.

While the prior art does recognize reduction of renal uptake of protein conjugates as evidenced by Behr et al (Cancer 80:2591-2610, 1997) which teach reduction using antibody conjugates labeled with agents and addition of D-lysine (see entire document), there is no indication in the specification or the prior art to indicate that unconjugated agents would have reduced renal uptake by adding D-lysine or poly-lysine. In addition, Behr et al (supra) discloses that the kidney is the primary dose-limiting organ in RAIT with Fab fragments but does not provide any indication that unconjugated agents would be retained in the kidney and need D-lysine or poly-lysine for lowering uptake in the kidney. In addition, the prior art does not indicate that metabolic products or peptides,

polypeptide, glycoproteins, lipoproteins, or antibodies are reduced when added with D-lysine or poly-lysine in the kidney.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

12. Claims 19, 38, and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 19 is indefinite for reciting "metabolic products thereof" because the exact meaning of the phrase is not clear. Does the phrase mean the conjugate is metabolized or broken down or the metabolic product is used as a conjugate or the metabolic product can be processed peptides? In addition, it is unclear if the agent is the metabolized product or if the protein part is the metabolized product. It is unclear what the phrase means and it is impossible to determine the meets and bounds of the phrase and claim.

b. Claim 38 recites said "imaging agent" in claim 38 and this phrase lacks antecedent basis in the claim.

c. Claim 40 is indefinite for reciting the trademark "ONCONASE" because the meaning of the name may be changed to refer to other compounds during the life of the patent. Also the name is not designated as a trademark. Amending the claim to recite the common generic form of the trademark as supported by the specification as

originally filed, would obviate this part of the rejection. Merely capitalizing the term does not overcome the rejection.

Claim Rejections - 35 USC § 102

13. Claims 1-8, 11-19, 23-28, 31-39, 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Behr et al (Cancer Research 55:3825-3834, 1995).

The claims recite a method of reducing kidney retention of a protein conjugate or in a patient undergoing treatment comprising administering D-lysine or poly-lysine of 15-30kD or a combination of two compounds and a protein conjugate to a patient and the protein conjugate is not greater than 60 kD, wherein the conjugate is a imaging isotope or a therapeutic isotope, wherein the solution is administered to the patient as a continuous infusion, i.v., i.p, orally, one injection or a continuous infusion, wherein the conjugate is a radiolabeled hapten conjugate. This rejection is made because the application is not grated the priority of the '899 application due to no support for the genus of proteins as indicated above and because an antibody is a protein. In addition, claim 38 is granted the priority of the instant application because of the new matter rejection and the art is being applied to what is enabled which is a protein conjugate comprising a cytotoxic or imaging agent (see above).

Behr et al teach a method of reduction of renal uptake of a protein conjugate of an antibody fragment of Fab' of which when conjugated is less than 60kD comprising an imaging or therapeutic moiety in a patient (mouse model) with addition of D-lysine and poly-lysine (15-30 kD) and the solutions were administered by iv or ip or orally and two

compounds were administered together (see entire document, especially abstract, page 3826, 3827, 3rd paragraph, 3830, left column first paragraph).

Claim Rejections - 35 USC § 103

14. Claims 1-9, 11-21, 23-29, 31-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Behr et al (Cancer Research 55:3825-3834, 1995), and further in view of Grey et al (U. S. Patent 5,380,513, issued 1/10/95, IDS #4) and Raines et al (U.S. Patent 5,840,296, filed 10/15/97).

Claims 1-8, 11-19, 23-28, 31-39, 41 have been described supra. Claims 9, 20-21, 29, 40, recite wherein the compound is poly-D-lysine, wherein the targeting protein conjugate is ONCONASE. This rejection is made because the application is not grated the priority of the '899 application due to no support for the genus of proteins as indicated above and because an antibody is a protein. In addition, claim 38 is granted the priority of the instant application because of the new matter rejection and the art is being applied to what is enabled which is a protein conjugate comprising a cytotoxic or imaging agent (see above).

Behr et al teach a method of reduction of renal uptake of a protein conjugate of an antibody fragment of Fab' of which when conjugated is less than 60kD comprising an imaging or therapeutic moiety in a patient (mouse model) with addition of D-lysine and poly-lysine (15-30 kD) and the solutions were administered by iv or ip or orally and two compounds were administered together (see entire document, especially abstract, page 3826, 3827, 3rd paragraph, 3830, left column first paragraph). Behr et al does not

teach a protein conjugate comprising a ribonuclease or ONCONASE. These deficiencies are made up for in the teachings of Grey et al and Raines et al.

Grey et al teach a method to reduce renal retention of protein conjugates with lysine (see abstract and column 3, lines 44 to column 4, lines 2). Grey et al teach the conjugates comprise imaging agents and therapeutic agents (see column 7), that comprise cytotoxins and the proteins comprise receptors and enzymes as well as other proteins (see columns 5-6) Grey et al also teach administration orally, iv, ip, or the like (column 6, lines 1-5).

Raines et al teach conjugates comprising ribonuclease which have been effective in tumor patients (see column 1) and the decrease in renal function of Onconase may be the consequence of an inability to effectively clear the Onconase protein from the kidneys (see column 2, lines 52-57). Onconase is a 104 amino acid protein (see column 2, lines 34-35) which is not greater than 60 kD.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al because Behr et al teach that kidney retention was reduced in conjugates by addition of lysine and poly-lysine

and that poly-lysine (15-30 kD) was more effective in reducing renal uptake and D-lysine should be metabolically inert (see page 3829 and 3832). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al because Grey et al teach that protein conjugates comprising enzymes and added lysine can reduce renal uptake of the conjugates. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al because Raines et al teach "A cytotoxic ribonuclease that is readily cleared from the kidneys would be less likely to cause renal toxicity" (see column 2, lines 58-62). Thus it would have been obvious to one of ordinary skill in the art to produce a method of reducing renal uptake of protein conjugates that comprise ONCONASE conjugates in view of the teachings of Behr et al, Grey et al, and Raines et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-9, 11-21, 23-29, 31-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-47 of copending Application No. 10/438,219. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the instant application encompass and anticipate the claims in the 10/438,219 application. Both claim sets are directed to methods of reducing kidney retention of a protein conjugate or agents by administering D-lysine or poly-lysine in the range of 1-60kD.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30

am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached at (571) 272-0787.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Larry R. Helms

571-272-0832